REMARKS

The specification on page 17, as originally filed, has been amended in accordance with the Office Action. The paragraph bridging pages 17 and 18 of the application, as originally filed, has been amended to remove the erroneous reference to "U.S. Pat. No. 4,976,957." Applicants continue to properly cite "application Ser. No. 07/744,649" for further explanation and support of the "immunological specificity" of malignin, Recognin L and Recognin M. No new matter is added by this amendment, which was made in the substitute specification filed July 27, 2001.

Claims 1 to 5 are pending. Claims 6 to 13 have been previously withdrawn by election in response to a restriction requirement. Claims 1 and 5 are herein amended.

Support for the amendments of claims 1 and 5 may be found throughout the application and, for example, in paragraph 12, where Applicants teach that anti-malignin antibody (also referred to as anti-Recognin antibody in the application, *see, e.g.*, ¶¶ 15, 17 and 24) has been shown to, among other things, be cytotoxic to malignant glioma cells, inhibit the growth of small cell lung carcinoma cells, be present on cancer cells removed at surgery, and (in view of the data provided in the application) act as a general inhibitory transformation antibody whose augmentation may be useful in efforts at the immune prevention and treatment of cancer.

Further support for the amendments of claims 1 and 5 may be found, for example, in Example 5 (paragraph 20) and in Figures 1J through 1L (the legends for these figures are found in paragraph 15). Example 5, and its supporting data in Figures 1J-1L, demonstrate the cytotoxic effect of antimalignin antibody on malignant glioma cells. The growth inhibitory properties of anti-malignin antibody in the range of picograms/cell are demonstrated in Example 6 and accompanying Figure 2 in small lung cell carcinoma.

Further support for the amendments of claims 1 and 5 may also be found, for example, in paragraph 16, which teaches that anti-malignin antibody has been shown to bind preferentially to malignant glioma cells in the rat brain *in vivo* when administered intravenously. Paragraph 16 further provides data establishing that anti-malignin antibody also binds in humans *in vivo* to adenocarcinoma, transitional cell carcinoma, neuroblastoma, and lymph node metastases. Paragraph 17 provides support for malignin derived from glioblastoma brain tumor cells.

A correlation between cytotoxicity *in vitro* and tumor cell killing *in vivo* had been demonstrated in the art by the priority date of this application. *See, e.g.*, Masui H. *et al.*, Cancer Res. 1989 Jul 1; 49(13):3482-8 (cytotoxic effect on human cell lines of antibodies against

epidermal growth factor receptor conjugated with ricin correlated with anti-tumor effect in mice); Stevenson, *Tumor Vaccines*, The FASEB Journal, Vol. 5, June 1991, pp. 2250-2257 at page 2252, left column (protection against tumor in mice provided by strong antibody response).

Together, the data disclosed in Applicants' specification provide full support for the methods and compositions of the claims.

A. OBJECTION TO THE SPECIFICATION

The Examiner has indicated that the citation to U.S. Pat. No. 4,976,957 on page 17 of the application, as originally filed, is improper because U.S. Pat. No. 4,976,957 did not issue from the properly cited application Ser. No. 07/744,649. Applicants have amended the specification herein to remove the erroneously cited U.S. Pat. No. 4,976,957. This error was removed in the substitute specification filed July 27, 2001. Because the error has been removed, Applicants respectfully request the Examiner withdraw this objection.

B. REJECTION OF CLAIMS 1 TO 5 UNDER 35 U.S.C. § 112, PARAGRAPH 2—DEFINITENESS

The Examiner has rejected claims 1 to 5 under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner asserts the claims do not imply a genus-species relationship for malignin, Recognin M, Recognin L or a peptide having the immunological specificity thereof. The Examiner asks that the claims be amended to show that the "peptide having the immunological specificity thereof" language be more clearly applied to all three species of the genus, namely, malignin, Recognin M, and Recognin L. Applicants have amended the claims to be directed to malignin. The amendments of claims 1 and 5 should render moot this rejection for indefiniteness. As such, Applicants respectfully request the Examiner withdraw this rejection.

C. REJECTION OF CLAIMS 1 TO 5 UNDER 35 U.S.C. § 112, PARAGRAPH 1—WRITTEN DESCRIPTION

The Examiner has maintained the rejection of claims 1 to 5 under 35 U.S.C. § 112, first paragraph, for failure of written description as set forth in the Office Action of February 15, 2005 at pages 6 and 7. There, the Examiner asserts the claim language "stimulating the immune system of a subject to produce and release antimalignin antibody" is new matter. The Examiner also requested submission of the Abstract of U.S. Appln. Ser. No. 08/031,562 to help clarify this language. Applicants regret that they have not located an Abstract in U.S. Appln. Ser. No. 08/031,562 to provide to the Examiner.

Nevertheless, as set forth in Applicants' response filed August 15, 2005, the application provides full support for the present claim language. Applicants have amended the claims to be directed to "a method for killing glioma cancer cells . . . comprising administering . . . malignin . . . wherein said administration . . . stimulates the immune system of said subject to produce and release antimalignin antibody that binds said glioma cancer cells and is cytotoxic to said glioma cancer cells." The claims as amended are supported, for example, by paragraph [003] of the application where Applicants teach "administration of . . . a derivative of a Recognin, to produce both the antibody and the cellular part of the immune response . . . ." One of skill in the art would understand "stimulating the immune system of a subject to produce and release antimalignin antibody" to be equivalent with "produc[ing] both the antibody and the cellular part of the immune response." One of skill in the art would have recognized that the language of the claims comports with the language of the application; and would consider the subject matter of claims 1 to 5 fully supported in the applications as filed.

Support for the presently amended claims is further found, for example, in example 8, which teaches that products having the immunological specificity of malignin can be administered subcutaneously as vaccines to humans or animals, and the quantity of antibody may be determined along with changes in B cells, T-cells, and macrophages, before and after the administration of vaccine. Applicants teach that the level of anti-malignin antibody will increase in the subjects approximately 10 days after the first administration of vaccine. Accordingly, Applicants submit that one of skill in the art would have understood that Applicants have taught stimulation of the immune system in Example 8.

Because Applicants fully disclosed the concept of administering malignin to stimulate the immune system, Applicants respectfully request the Examiner withdraw this rejection.

D. REJECTION OF CLAIMS 1 TO 5 UNDER 35 U.S.C. § 112, PARAGRAPH 1—Enablement

The Examiner has rejected claims 1 to 5 under 35 U.S.C. § 112, first paragraph, for failure to comply with the enablement requirement because the previous claim language "which process does not by itself protect against or treat cancer" did not overcome the previous rejections. Applicants have amended the claims to remove this language. As such, the Examiner's rejection over that particular language should be moot.

In the Office Action of February 15, 2005, the Examiner rejected the claims for lack of enablement because the full scope of the claims "involves immunizing (vaccinating) against any

type of cancer." This rejection was based upon the decision of the Board of Patent Appeals and Interference in the parent case mailed November 30, 2000. *See* Office Action of February 13, 2006 at page 4. The Examiner further found, in considering the Wand's factors: (1) "extremely broad" claims; (2) a lack of working examples; (3) no similar antibodies in the art that successfully treat cancer; and (4) and "high unpredictability" in for antibodies. The Examiner acknowledged under the Wand's factors, however, that the level of skill in the art of cancer treatment was very high.

Applicants respectfully submit the claims as amended obviate the rejections for lack of enablement. The claims as amended are directed to a method for killing glioma cancer cells where the cancer cells express malignin and administration of malignin stimulates the immune system of a subject to produce and release antimalignin antibody that binds to and is cytotoxic to glioma cells. As discussed above, the application as filed teaches antimalignin antibody that is cytotoxic to glioma cancer cells and binds specifically to glioma cancer cells *in vivo*. *See* Appln. at ¶¶ 12, 15, 16, 20 and Figures 1J-1L. The application further teaches the administration of malignin to stimulate the immune system to produce these antibodies. *See id.* at Example 8. The application additionally teaches the binding of these antibodies in human tissue and increased survival rate for humans having higher concentrations of the antibody. *See id.* at Example 7. As further discussed above, the art contained teachings of *in vitro* cytotoxicity in antibody preparations that correlated with killing malignant cells *in vivo*. Finally, antibodies to tumor antigens have been shown to kill cells in humans just as taught by Applicants. *See, e.g.*, FDA approved Rituximab™.

In view of the extensive teachings and data provided by Applicants with respect to the killing of glioma cells, Applicants respectfully request the Examiner withdraw the rejection for lack of enablement.

E. REJECTION OF CLAIMS 1 TO 5 UNDER 35 U.S.C. § 102(b)—Anticipation

Claims 1 to 5 have been rejected as anticipated over U.S. Pat. No. 4,976,957 to Bogoch and claims 1 to 3 and 5 have been rejected as anticipated over EP 0,015,078 to Bogoch. The Examiner asserts the patents "teach preparations of malignin, Recognin-M or Recognin-L for the immunization of animals, in order to produce antibodies thereto." The claims, as amended, are directed to a method of killing glioma cells in a subject. The cited art does not teach the killing of glioma cells in a subject.

Because the cited art does not teach or suggest every element of the claims, applicants respectfully request the Examiner withdraw the rejection.

F. REJECTION OF CLAIM 1, 3 AND 4 UNDER 35 U.S.C. § 103(a)—Obviousness

Claims 1, 3 and 4 have been rejected over Bogoch (US '957 and EP '078) in view of Chase. The Examiner asserts "Chase shows a variety of immunization regimens." None of the cited art together teaches the killing of glioma cells in a subject. As such, the combination of the art should not render the currently amended claims obvious.

Because the cited art in combination does not teach or suggest every element of the claims, applicants respectfully request the Examiner withdraw the rejection

CONCLUSION

It is believed that the present claims are in conditions for allowance and Applicants earnestly request allowance. Extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to Kenyon & Kenyon LLP **Deposit Account No. 11-0600**. The Examiner is invited to contact the undersigned attorney if necessary to expedite allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

KENYON & KENYON

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Teresa A. Lavenue
Reg. No. 47,737

1500 K Street, N.W.- Suite 700
Washington, DC 20005
Telephone: 202/220-4200
Facsimile: 202/220-4201